

# SARS-CoV-2 and the Guillain-Barré syndrome – features for a complex association

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## ABSTRACT

**Background.** Guillain-Barré syndrome (GBS), the most common cause of flaccid motor deficit with acute or subacute onset, is associated in approximately 2/3 of cases with a history of microbial, predominantly viral, infection. In the context of the current COVID-19 pandemic, the presence of patients with both peripheral nervous system pathology and SARS-CoV-2 viral infection raised questions among researchers whether there may be a possible link between the two entities. Thus, this narrative review aims to provide a clearer perspective on this topic, addressing several issues.

**Methods.** The authors performed independent research of the available literature in the most important electronic databases (PubMed, Google Scholar, and Science Direct). After applying the exclusion criteria, the reviewers focused on the most relevant articles published during the last 18 months, focusing on epidemiological and pathophysiological data regarding GBS and COVID-19.

**Results.** In the first part, a summary of the most important results from the literature on the epidemiological situation in different parts of the world was conducted. Subsequently, possible immunological theories are presented in order to explain the epidemiological association between GBS and COVID-19 infection. Finally, the authors propose new research directions on the topic, discussing the issue of the COVID-19 vaccine, with its short and long term effects, and possible correlations with peripheral nerve pathology.

**Conclusion.** Neurological manifestation in COVID-19 may represent a challenge for the clinician, and with growing numbers of unprecedented cases of peripheral nerve pathology associated with the SARS-CoV-2 virus being reported, further research is urgently needed.

**Keywords:** Guillain-Barré syndrome, SARS-CoV-2, COVID-19, autoimmunity, pathophysiology, COVID-19 vaccination

## Abbreviations

ACE2 – angiotensin-converting enzyme 2

AIDP – acute inflammatory demyelinating polyneuropathy

AMAN – acute motor axonal neuropathy

AMSAN – acute motor-sensory axonal neuropathy

CIM – critical illness myopathy

CIP – critical illness polyneuropathy

CNS – central nervous system

GBS – Guillain-Barré syndrome

IVIG – intravenous immunoglobulin

PNS – peripheral nervous system

RT-PCR - reverse transcription polymerase chain reaction

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## INTRODUCTION

Guillain-Barré syndrome (GBS), the most common cause of acute tetraplegia worldwide, remains an insufficiently characterized disease, at least regarding its etiology and pathophysiology [1]. Although the exact cause of this syndrome is still unknown so far, two aspects are well defined. On the one hand, much of the autoimmune cascade responsible for damage to the peripheral nervous system has been identified. On the other hand, in over 50% of GBS cases, patients developed a most commonly viral infection a few days-weeks before installing neurological symptoms [2]. Among the microorganism that predispose to GBS, we mention: *Campylobacter jejuni*, Epstein-Barr virus, Influenza virus, and more recently Zika virus [3]. In addition to epidemiological studies that have reported this link, more and more research in the field of pathophysiology and immunology confirms the local and systemic effects of microorganisms in the peripheral nervous system (PNS), at least partially explaining GBS's etiology.

The current COVID-19 pandemic, by spreading rapidly all over the world and causing severe medical problems to the population, has brought a new challenge for physicians in all medical specialties. In addition to the predominant involvement of the respiratory tract (i.e. COVID-19 pneumonia), numerous neurological complaints have been observed in COVID-19 patients [4]. Studies conducted during the last year have shown both central (stroke, demyelinating myelitis, headache) and peripheral nervous system pathology (GBS, CIM, CIP) in SARS-CoV-2 infected patients [5]. This correlation between COVID-19 infection and acute inflammatory polyneuropathy has been investigated in different parts of the world, resulting in different, sometimes contradictory, epidemiological data. Thus, one purpose of this article is to present the most important epidemiological aspects on this topic and to find, a direct link between the two clinical phenomena, if existing.

In order to explain the epidemiological data, it was necessary to develop new pathophysiological and immunological theories to better detect the way SARS-CoV-2 virus could act at the peripheral nerves level, producing both demyelinating and axonal destruction. Thus, in the second part of this article, the authors made a synthesis of the currently available hypotheses in the scientific world regarding the autoimmunity mechanism through which SARS-CoV-2 is capable of producing acute flaccid paralysis.

Corroborating both the epidemiological data and the immunological mechanism, in the last part of the paper, the authors suggest possible future research directions. Starting from the current knowl-

edge gaps, discussions arise regarding the issue of the COVID-19 vaccine, focusing on the benefits and possible complications that may appear and directly affect the peripheral nervous system.

## MATERIALS AND METHODS

In order to achieve the aim of this article, the most important electronic databases (PubMed, Google Scholar, and Science Direct) were searched for articles published in the English language mostly from January 1, 2020 to present, involving human subjects, but also other articles were included in this review if relevant. The authors have done independent searches during April and May 2021, using the following combination of terms: („COVID-19” OR “SARS-CoV-2”) AND (“Guillain-Barré syndrome” OR “Landry-Guillain-Barre syndrome” OR “acute inflammatory polyradiculoneuropathy”).

After applying the exclusion criteria (non-English language, abstract only articles, animal researches, non-COVID-19 trials), the reviewers focused on the most relevant articles published during the last 18 months, with respect to epidemiological, clinical and paraclinical featured, pathophysiology and COVID-19 vaccine.

## EPIDEMIOLOGICAL, CLINICAL AND PARACLINICAL EVIDENCE REGARDING THE COVID-19 – GBS ASSOCIATION

Since the onset of the current pandemic, clinicians have faced challenges in treating COVID-19 patients, especially cases associating extra pulmonary pathologies in addition to positive RT-PCR testing for SARS-CoV-2 virus [6]. One common complaint was the acute onset of flaccid paralysis as a manifestation of peripheral nerves pathology, more precisely, a form of GBS. Causing immobilization, with increased risk of thrombosis, pulmonary stasis, GBS worsens of the general condition of the already fragile COVID-19 patient [7].

From the beginning of the pandemic until present, numerous COVID-19 patients suffering from GBS have been reported [8]. However, it must be said that, given the relatively short period of time (just over a year), after a careful research of the available literature, most published works are case reports, sometimes series of several cases. Only few retrospective clinical trials or systematic reviews comprising a large number of patients exist today, most having been published during the last months. Although case reports remain important as starting points for future detailed research, presenting either patients with unusual forms of GBS, or describing unexpected outcomes after different treatments, systematic reviews and meta-analysis deliver the

most informative data on this new topic and help clinicians create good clinical practice guidelines for the future.

When thinking of epidemiological data related to GBS and COVID-19, one must consider several characteristics, from personal traits such as gender, age, or associated comorbidities, to disease-related aspects like the clinical phenotype of GBS and outcome to specific treatment.

Summarizing currently published literature, all systematic reviews consulted showed a higher incidence of the disease in males [9-18], with different percentages according to case selection. Age seems also to be a predisposing factor, GBS being encountered in elderly COVID-19 patients. Mean age of symptoms onset ranged according to author, however, most reports included patients of age 50 and more. GBS can also be found in children, as the case of a 12-year-old child with initial cardiopulmonary degradation, coma, resuscitation and endotracheal intubation in the intensive care unit (ICU), which favorable evolution under subsequently IVIG therapy, with the remission of the abovementioned symptoms and the amelioration of the motor deficit [19].

Also related to individual profile, some authors found important to correlate GBS post COVID-19 with patients' prior comorbidities. According to current available literature, hypertension and diabetes mellitus type 2 are among the most prevalent [9,16], one explanation being the fact that most patients involved are males over 65-years of age, having higher risk of developing cardiovascular pathologies.

The geographical influence on the unequally distributed incidence of COVID-19 associated GBS should not be neglected. In this regard, the work of Widyadharma et al. shed light on the situation in Asia, with 9 articles referring to neurological manifestations in COVID-19 patients, with only two case reports describing GBS symptomatology [20]. However, given the scarce data related to this subtopic, there is a high chance current results are biased, new studies on evaluating the influence of other environmental factors and genetic parameters are needed.

Regarding the disease status and evolution, classical GBS symptoms are also common in COVID-19 related GBS. Thus, sensory disturbances (paresthesia and hypoesthesia) combined with ascending motor paralysis is the rule, with either para or tetraplegia as main motor neurological complaints. In rarer cases, when cranial nerves are involved, symptoms like dysphagia, dysarthria, and diplopia may also be encountered, alone or together with other neurological signs outlining the clinical picture [15]. Of interest for treatment choice and long-

term outcome, we mention the association with non-neurological complaints. The arbovirus has high tropism for the respiratory system, consequently, respiratory symptoms are the most frequently encountered, with dry cough, anosmia, sore throat, fever and shortness of breath as the most prominent ones [11,14]. Yet, as SARS-CoV-2 has the ability to reach multi-systemic affection, gastrointestinal symptoms, headache, and cutaneous rash may also be found [16,17].

However, one must not forget that the symptomatology related to GBS can sometimes be misleading. Either GBS may be mimicking other completely unrelated pathologies, or vice-versa, other neurological or systemic diseases can contain in their clinical picture specific GBS symptoms, such as paraplegia or tetraplegia [21]. This particular clinical aspect must be taken into consideration also in the context of the current pandemic, as there have been reported some atypical cases of GBS in the literature. We mention cranial nerve involvement under different forms, as observed also in the work of Uncini et al., where among 42 patients, 3 suffered from facial diplegia, 3 were diagnosed with the Miller-Fisher's variant, and 2 had other cranial polyneuritis [18].

The electrodiagnosis of GBS post COVID-19 do not differ much from the classic forms of non-COVID-19 GBS. All meta-analyzes found acute inflammatory demyelinating polyneuropathy (AIDP) as the most common form [10-18], in cases where electrophysiology studies were performed. In a minority of cases, electrodiagnosis has also confirmed other forms of GBS, mainly axonal destructions, such as acute motor-sensory axonal neuropathy (AMSAN) or acute motor axonal neuropathy (AMAN) [9,15].

Another biological evaluation of interest was CSF analysis, which in over 80% of cases detected an albuminocytological dissociation [14], while in the other patients the evaluation remained within normal parameters. Evaluation of the presence of SARS-CoV-2 virus in CSF remains a controversial topic, with the majority of CSF analysis obtained after lumbar punctures being negative for RT-PCR testing for this virus [10]. Imaging examinations may be an adjuvant tool in the diagnostics of COVID-19, with chest X-ray or chest CT as the most used investigations [15,16]. Regarding specific imagery investigations for confirming neurological complaints, in only a minority of cases cranial nerve or spinal nerve root enhancement was observed, with unremarkable results being the rule [11].

Time latency after initial infection is another important point when referring to GBS associated with COVID-19. If GBS appears commonly 10 days after COVID-19 infection [13], there may be also late-onset cases. In his article, Zubair et al. present two cas-

es of patients who suddenly installed acute flaccid paralysis 8 weeks after infection with SARS-CoV-2 virus [22]. According to the authors, the differential diagnosis with critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) should be made, especially in patients who have been treated in the ICU for a prolonged time. Another example is the case of a 46-year-old man with no significant pathological history before COVID-19 infection, who acutely installed GBS symptomatology 53 days after COVID-19 pneumonia, the authors considering a possible long COVID syndrome [23].

Treatment options was another key-element discussed in all systematic reviews, a general tendency among clinicians being the use of intravenous immunoglobulins (IVIG). Most cases responded well to this treatment, with good recovery [9-18]. Sometimes, IVIG are not enough, patients needing ICU admission and endotracheal intubation, with additional therapeutic measures mandatory. Thus, plasmapheresis remains a valuable option in the case IVIG cannot be administered, or together with IVIG in critical patients [15,16]. Moreover, some mild cases did not receive any of the aforementioned therapies, instead, either no treatment was needed, or drugs such as hydroxychloroquine were employed [11].

Clinical outcome remains essential for the patient and family, partial to complete recovery being noted in many cases when longer follow-up was conducted. Lack of motor symptoms improvement must be however taken into consideration, a minority of cases also reporting the death of the patient [12,17]. A limitation in this direction is the short-term follow-up encountered in many case reports on this topic, one possible explanation being the unexpected epidemic development. Along acute and supportive treatment, respiratory and neurologic rehabilitation are mandatory needed in the case of COVID-19 patients affected also by GBS.

Compared to other neurological symptoms or pathologies related to COVID-19 infection, GBS does not seem to be associated so frequent. At least this would be the conclusion of Amanat et al., who conducted a prospective multicenter study on a cohort in Iran, summing 873 cases of SARS-CoV-2 infected patients having additionally neurological symptoms, of which only one presented GBS symptomatology, with good evolution after treatment [24].

Sometimes, in COVID-19 patients, an overlap of central and peripheral nervous system pathology can occur, with a higher impact and severity compared to non-COVID-19 patients. One such example is the case report of Ansari and Hemasian, which presents the situation of a patient who suffered simultaneously from GBS and stroke, with satisfactory evolution in the end [25]. However, the associa-

tion of the two distinct pathologies indicate that COVID-19 infection may not always remain asymptomatic, while the clinician must take into account particular situations, rarely encountered in clinical practice before. A bizarre situation has also been mentioned by Collona et al., in a patient with concomitant GBS symptoms and in MRI confirmed CNS vasculitis-like lesions, both findings considered to be a form of dysimmune response involving the nervous system [26].

Despite the evidence presented, including studies in large patient groups, there are also data contradictory data in the literature, as some authors did not find any statistically relevant epidemiological correlation between COVID-19 infections and a possible increase in the incidence of GBS. For example, Umapathi et al. described the situation in Singapore in 2020 [27]. There has been a decrease in the incidence of GBS hospitalization compared to the previous year, with only one case of AMAN subtype GBS being documented between January and October 2020. Similar results were also reported in the work of Keddie et al., as no epidemiological data sustained an association between SARS-CoV-2 and GBS in the UK studied population [28].

As COVID-19 is a recent pathology with still many unknowns, new studies on larger cohorts of patients are needed in order to have a more accurate picture of the real epidemiological data of neurological complications, especially GBS, in COVID-19 patients.

## **IMMUNOLOGICAL AND PATHOPHYSIOLOGICAL THEORIES SUSTAINING THE GBS – COVID-19 ASSOCIATION**

A little over a year old, the COVID-19 pandemic has brought important changes in all medical sub-fields, with all organs and systems of the human body being possible targets for SARS-CoV-2 virus. Moreover, peripheral and central nervous systems are preferred locations for coronavirus settlement and potential destructive changes may occur at this levels. Although the pathophysiological and immunological mechanisms are not fully understood yet, researchers have already generated several explanatory hypotheses on the tropism and influence of SARS-CoV-2 in the nervous tissue, two main theories standing out.

The first theory refers to the receptor-mediated pathway. SARS-CoV-2 virus is thought to cause GBS symptomatology in some patients directly, attaching to angiotensin-converting enzyme 2 (ACE-2) receptors located in neuronal tissue, as it is demonstrated that the virus has high neuro tropism and invasive capability [29]. The direct pathway is more specific for CNS infections, SARS-CoV-2 invading the



brain via the olfactory bulb, passing through the nostrils in different areas of the brain. At that level, using the transmembrane serine protease 2 (TMPRSS2) to initiate protein S and subsequent pathway, the virus will manifest its pathogenicity. The same principle seems viable in the case viral transmission via enteral route, SARS-CoV-2 having tropism at the gastrointestinal system level due to the high expression of ACE2 receptors. Once CNS invaded, the virus can spread to the PNS, causing acute, subacute or chronic cranial nerve pathologies. As serological evidence for this direct invasion mechanism, we mention the negative results of antibody testing in patients with COVID-19 and Miller Fisher syndrome, arguing more for viral neurotropism cause of the symptoms than by immune-mediated lesions [4].

The second theory pleads for an indirect, humoral pathway, based mainly on the immune system response and is the most important mechanism with explains SARS-CoV-2 pathogenicity [30]. The aggressiveness of the virus, which is clinically translated by the acute respiratory distress syndrome (ARDS) or haemophagocytic lymphohistiocytosis (HLH) [31], is mainly due to hyper stimulation of the immune system. COVID-19 infection has been shown to cause an immune reaction with elevated levels of interleukin-6 (IL-6), a cytokine that stimulates the inflammatory cascade, thus producing damages at nerve tissue level. Other proinflammatory cytokines (IL-1 $\beta$ , IL-10, IL-17, TNF) and other inflammatory markers such as ferritin have also shown significant increased values in COVID-19 patients, regardless of the severity of the clinical picture [32]. These mechanisms may promote the emergence of new autoimmune diseases, such as immune-mediated neuropathy (GBS), autoimmune thyroiditis, or autoimmune vasculitis in both adults and children.

Also in close connection with the indirect pathogenicity mechanism of SARS-CoV-2, of great importance remain the autoantibodies generated as a result of molecular mimicry mechanism (but not only) following the primary infection [33]. The most relevant markers are antibodies to cardiolipin (aCL), lupus anticoagulant (LAC) and antibodies against beta2 glycoprotein I ( $\beta$ 2GPI), high values explaining the phenomena of disseminated intravascular coagulation commonly found in patients [34]. Although at present still incompletely explained, these immune-mediated changes, among other still unknown diverse mechanism, surely play a central role in the direct link between COVID-19 infection and associated neurological symptoms.

## FUTURE PERSPECTIVES AND COVID-19 VACCINES

Having a short duration of just over a year, the current COVID-19 pandemic has not given research-

ers enough time to study in detail the pathophysiological and immunological pathways that explain the ability of SARS-CoV-2 to cause neurological problems in addition to pulmonary damage. Case-control studies or small series of cases are good as a starting point, but conducting randomized studies with a large number of patients and comparison with a statistically significant control group is essential for the validity of scientific data. One important direction to follow in future studies is, besides gathering already published data, adding more preciseness in evaluating this association, by conducting a comparison between different geographical areas, specific environmental and hereditary factors that may influence apparition, evolution and outcome of GBS in COVID-19 patients.

In addition, possible future mutations of SARS-CoV-2 mean many unknowns for the future, so the medical world must remain alert to any neurological or non-neurological manifestations associated with prior COVID-19 infection. If so far, most cases of GBS in the COVID-19 context have had a satisfactory response to standard therapies (IVIg or plasmapheresis), this is not a guarantee that new mutations will not cause more severe manifestations. Thus, another research perspective would be the development of new treatments that are more effective and have fewer related side effects. Moreover, it would be of great importance if the new medication could have a double cumulative effect, both for improving neurological conditions and diminishing viral viability.

Perhaps the most important perspectives are those related to COVID-19 vaccines, a new, expanding field in which the long-term consequences are still unknown. From the point of view of PNS pathologies possibly correlated with vaccines, the possibility of developing a post-vaccine GBS should not be omitted. The possibility of developing GBS as a related side effect after vaccination is known, e.g. influenza vaccine. Regarding both the mRNA technology-based and vector-based COVID-19 vaccine, the literature notes the very low but possible risk of developing neurological adverse effects. A recent example is the case reported by Waheed et al. of a 82-year-old female who developed GBS two weeks after administration of the first dose of mRNA technology-based COVID-19 vaccine [35]. Another interesting case report refers to a 73-year-old, active smoker and hypertensive male who developed GBS 20 days after receiving the second dose of Pfizer COVID-19 vaccine, with full recovery after IVIg and physical therapy [36]. However, data from a large cohort from Mexico receiving mRNA technology-based COVID-19 vaccine show that GBS is an infrequent adverse reaction, GBS timely related to COVID-19 vaccine being found in patients were con-

current infectious triggers such as gastrointestinal infections were detected [37].

Regarding vector-based COVID-19 vaccine, we mention the case presented by Finsterer, when a 32-year-old male developed Guillain-Barré syndrome 8 days after receiving the first dose [38]. Another report by McKean & Chircop of a 48-year-old man who developed bifacial weakness temporally related (10 days after receiving the first dose) to the Vaxzevria vaccine is also worth to be mentioned [39]. Indeed, compared to mRNA vaccines, in persons receiving adenoviral based vaccines a small (1.4-to-10-fold) rise in the incidence of GBS was observed, according to a small series of cases reported by Maramattom et al. [40].

An issue not completely clarified yet is whether GBS related to COVID-19 vaccination differs in terms of clinical picture, evolution and outcome compared to COVID-19 GBS. The scarce literature available at present could suggest that GBS occurs more frequently in vaccinated women than in men, as opposed to epidemiological data related to GBS associated with COVID-19 infection [40]. Neurologic symptoms occur most often 10 to 14 days after vaccination and consist of heterogeneous clinical pictures, including sensorimotor complaints in limbs and also frequent cranial nerve damage (facial diplegia, bulbar palsy) [41]. Atypical onsets, such as papilledema are also possible, a causal relationship being demonstrated in one case report [42]. Demyelinating neuropathy is the most frequent form diagnosed through EDX, however other types such as AMSAN may also be found [43]. Clinical course is milder compared to COVID-19 related GBS, patients experiencing almost complete recovery after IVIG and physical treatment, which has to be promptly administered. One paper tracing prediction on the topic showed that older age and association of some vaccine adverse effects such as paresthesia and apnea imply a higher risk of developing GBS [44], however only long term follow ups will confirm this predictive data. Therefore, in addition to the undeniable benefits that the vaccine has for all mankind, it is necessary to follow closely and promptly report

adverse reactions, with acute installed GBS being one of them.

## CONCLUSIONS

GBS, a rarer neurological disorder, remains of interest for the neurologist, especially since its exact etiology is still only partially explained. The current COVID-19 pandemic has demonstrated by the presence of new reported GBS cases that further research is needed in order to completely understand the link between these two pathogenic entities. The question remains whether there really is a link between them, or whether the reported cases are just statistical or epidemiological coincidences. On the other hand, the pathophysiological data based on two strong theories argue for an autoimmune mechanism as the base for SARS-CoV-2 to play a triggering role for neurological pathology.

Even if in most of the reported cases, the classical demyelinating form of GBS with effective response to IVIG therapy was encountered, there were also unprecedented forms reported, that pose a challenge for the neurologist. Future unknown mutations of the virus bring many uncertainties regarding diagnosis and treatment, thus, it is mandatory to conduct further in-depth studies on the association between GBS and COVID-19 infection.

Finally, the emergence of the new COVID-19 vaccines opens new perspectives with obvious benefits for the general population. However, the attention of researchers and clinical rigor must not diminish, with short and long term vaccine related neurological side effect mandatory to be taken into consideration.

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The authors acknowledge that the main limitation of this review is not to present all cases of GBS in the COVID-19 context, an almost impossible task, as long as new case reports on this topic appear almost daily. In this regard, we apologize to the authors whose works are not mentioned in this review.

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